The role of ultrasonography and magnetic resonance imaging in early rheumatoid arthritis

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ABSTRACT

Advances in ultrasound (US) and magnetic resonance imaging (MRI) techniques have provided new methods for evaluating early rheumatoid arthritis (RA). Their diagnostic properties in terms of detecting primary pathology of RA (i.e., erosions, bone changes, synovitis, tenosynovitis, and effusion) are reviewed. High-resolution US plays a significant role in therapeutic and diagnostic procedures. MRI also assists in the understanding of RA pathogenesis and joint mechanics.

Introduction

The rationale for early diagnosis and the recent availability of new, expensive targeted therapies, particularly for patients with rheumatoid arthritis (RA), have driven the need for sensitive imaging techniques that can be used not only to accurately diagnose the disease and provide prognostic information but also to monitor the efficacy of new therapies (1). Technological advances and the increasing availability of new imaging techniques, such as high-resolution ultrasound (US) (2-7) and magnetic resonance imaging (MRI) (1, 8-10),have provided exciting new possibilities for the assessment of early RA (11, 12).

ULTRASONOGRAPHY

The role of ultrasonography in the management of patients with early RA is discussed with regard to diagnostic properties,assessment of treatment responses and future developments. However, much of the literature relates to patients with established RA.

US: Diagnostic properties
Detection of bone erosions (Fig. 1)
Alassarela *et al.* (13) compared conventional radiograph (CR), MRI and computerised tomography (CT) with US in a preliminary study assessing erosions of the humeral head in patients with RA. They found that MRI, CT and US were all more sensitive than CR, with MRI and US superior to CT in detecting small erosions. Backhaus *et al.* (14) compared CR, MRI, scintigraphy and US in the finger joints (wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints) of 60 inflammatory arthritis patients, 36 of whom had RA and did not demonstrate a superiority of US over CR, a finding which may possibly reflect the analogue technology used (15) or the assessment of the wrists and PIP joints which may also have degenerative changes, making interpretation of bone damage difficult sometimes. A recent published 2 year follow up study of these patients, however, did show a benefit of US over CR (16).

A study by Wakefield *et al.* (17) compared US and conventional postero-anterior (PA) radiography for the detection of erosions of the MCPJ of 100 patients with RA (40% had disease duration of < 12 months). The study found that US was a reproducible technique and detected 3.5 times as many erosions as radiography; this difference was even greater in those with early disease. The superiority of US over CR is explained by the multi-planar capability of US and the fact that US can detect smaller erosions. This latter point may be particularly important in early RA. To help evaluate the pathology of these additional US erosions, MRI was used to assess the radial aspect of the 2nd MCP heads in 25 patients with early disease. One radiographic erosion was seen which corresponded exactly with both US and MRI lesions. All 10 MRI erosions corresponded exactly with an US erosion. Interestingly US detected 3 additional erosions. These findings can be explained by the superior spatial resolution of US compared to MRI and the potential voluming effect of MRI. This finding has been confirmed by a more recent study by Alarcon *et al.* (18). The superiority of US to detect
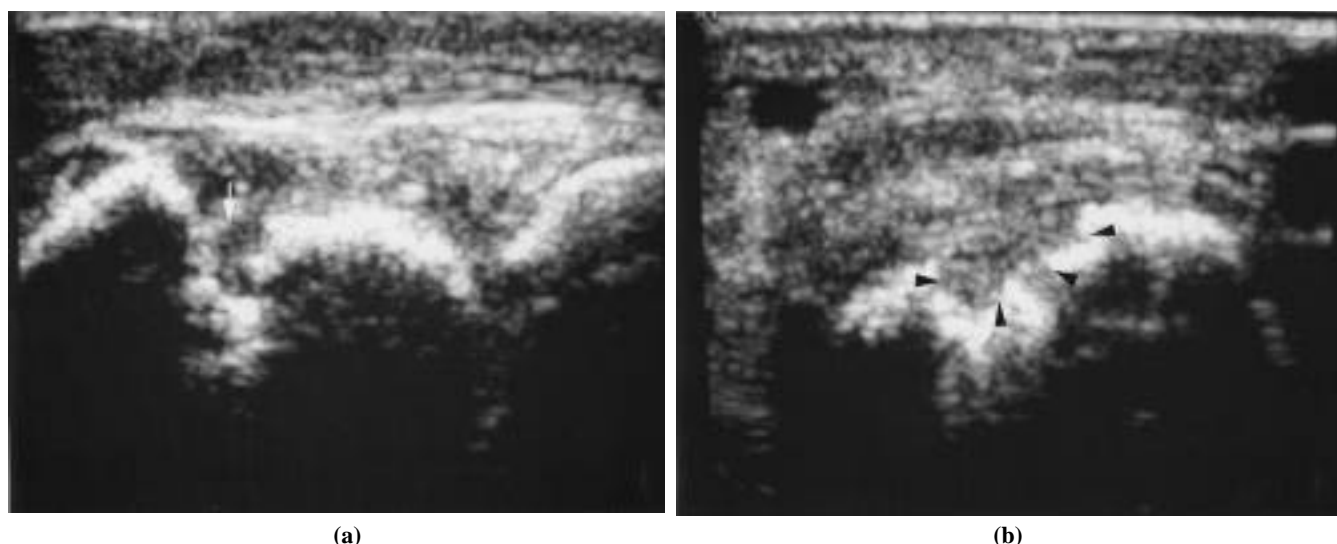
| (a) | (b) |

Fig. 1. Erosion (**arrow**) visible at the metacarpophalangeal joint of a patient with early rheumatoid arthritis in longitudinal (**a**) and transverse (**b**) views.

smaller erosions has also been described by Grassi *et al.* (19) in the hands and Klocke *et al.* (20) in the feet. Both also highlight the lateral aspect of the 5th MTP joint as a target in RA. In a recent study of 47 patients with RA, Weidekamm *et al.* (21) found twice as many erosions in the wrists, MCP joints and PIP joints by US as CR. The authors did not comment on how many patients had early disease.

In our own early arthritis clinic, US has not replaced radiography for the assessment of early bone damage. It is used instead as a complementary tool for assessing those patients at high risk of an inflammatory arthritis in whom radiographs are normal or for re-examining indeterminate lesions detected on radiography (22).

Detection of synovitis/tenosynovitis
(Fig. 2)

Many studies have highlighted the ability of US to detect early synovial disease in both large and small joints and its superiority over clinical examination (14, 23, 24). An increasing number of these had attempted to validate US against arthroscopy, MRI and scintigraphy. An early study by Van Holsbeeck *et al.* (25) compared clinical assessment with thermography and US for the assessment of knee synovitis and joint fluid in patients with RA, pre and post intra-articular joint injection with corticosteroid. They found that the volume of synovial fluid as assessed by US correlated well with the clinical assessment although it was 3 months before the synovial fluid demonstrated any significant reduction in volume. Back-

haus *et al.* (14), in a study of 60 patients with inflammatory arthritis, found more synovitis in the joints of the hand and wrist with US when compared to radiography and clinical examination and it was comparable with MRI.

While most studies have employed a grey scale, more recently power Doppler (PD) has become increasingly popular with the advantage of being able to assess synovial vascularity. Validation of PD has been assessed by comparison with histopathology in the knee in RA and OA (26, 27) and dynamic MRI in the MCP joints in RA (28) with encouraging results. PD has also been successfully used to assess inflammatory disease activity in RA (29, 30) and monitor response to treatment (31, 32). The sensitivity of PD may be further enhanced by intra-vascular microbubble contrast agents which raise the intensity of weak signals to a detectable level (33, 34). Magarelli *et al.* (35) in a study of 40 patients with inflammatory arthritis showed that the use of echo-contrast agents resulted in an increase in the Doppler signal intensity in joints with a previously low signal, together with an increased number of joints demonstrating PD flow, which previously had no signal. They also demonstrated concordance with contrast enhanced MRI in all cases. Other studies have reported a similar increase in the detection rate of Doppler signal flow using this technique. Interestingly,
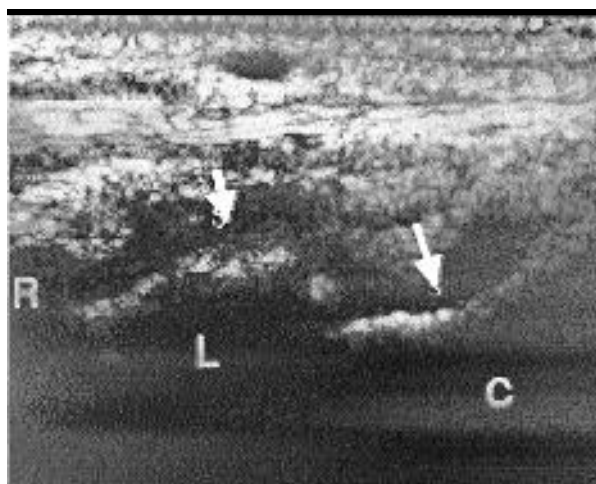

Fig. 2. Synovial hypertrophy (**arrow heads**) is demonstrated in the wrist joint of a patient with early RA. **R**: radius; **C**: capitate; **L**: lunate.

a published paper by Szkudlerek *et al*. (36) comparing PD and contrast-enhanced PD US suggests that PD is reliable for the assessment of synovitis in MCP joints of patients with RA; intravenous contrast agents only provided additional information in selected cases and did not increase the overall sensitivity of the method.

A further use of US and MRI in the detection of synovitis has been highlighted by Brown *et al*. (37). In their study of patients with RA in clinical remission as defined by the ACR criteria (38), almost half the patients had signs of sub-clinical synovitis in joints not thought to have any clinical synovitis. Another group of investigators (39) have used PD to assess the prognosis of early RA patients receiving anti-TNF therapy. They concluded that the power Doppler signal predicted the future risk of developing erosive disease.

US has also been used to detect tendon disease in RA. Grassi *et al*. (40) described the spectrum of pathological features seen in 20 patients with RA, including widening of the flexor tendon sheath, loss of the normal fibrillar architecture, tears and synovial cysts. Swen *et al*. (41) assessed the value of both US and MRI for the detection of partial tears of the extensor tendons of the hand in 21 patients with RA. They concluded that neither had the required sensitivity for routine use when surgery was used as the gold standard.

Detection of extent of disease
In a recent study of 80 patients with oligoarthritis (42), two-thirds of the patients had sub-clinical synovitis detected on US and one-third could be reclassified as having a polyarticular disease. Among the 12 patients who were rheumatoid factor positive at baseline, 83% had evidence of sub-clinical synovitis on US imaging. Of note, only 9% (1/12 patients) fulfilled the ACR criteria for RA at baseline, but the addition of US findings (synovitis and erosions) increased this percentage to 50% (6/12). This finding demonstrates a potential role for US in assisting in the early diagnosis of RA and highlights an advantage over MRI (i.e., the ability to scan several joints at one time point).

US: Diagnostic and therapeutic procedures
US guided joint aspirations are frequently performed to evaluate for the presence of infection or crystal disease (43) to assist in clarifying the diagnosis. The majority of joints can be aspirated under direct visualisation of the needle. The hip is the most common joint requiring US-guided aspiration. On occasion US-guided hip aspiration can be difficult in the adult, as lower frequency (3-5 MHz) transducers are required to achieve the beam penetration necessary to visualise the hip, resulting in poorer image quality.

Diagnostic and therapeutic aspirations/injections are of value in the assessment of both joint disease and soft-tissue lesions. Diagnostic injections are those performed into or around a structure where local anaesthetic is instilled to determine whether the patient's symptoms arise from that area. Two published studies showed extremely poor accuracy of joint injections without imaging guidance and reported an accuracy of 42% to 51% for large joint injection and only 29% for subacromial bursal injections (44, 45). For these injections to be of reliable diagnostic and therapeutic value, the exact site of injection must be known. US can and should help clarify this situation by both delineating the abnormality present and recording the site of injection. US allows the operator to dynamically image the needle placement and the distribution of any injection performed (46, 47).

As the value of the macroscopic appearance of arthroscopic synovitis in the management of early RA remains uncertain, US may have a role to play in guided biopsies in an outpatient setting (48) and several centres are currently exploring its feasibility and value.

US: Future developments
Technological advances in US are continually improving image quality and contrast between tissues. Good interobserver correlation has also been recently demonstrated in a paper studying the detection of synovitis and bone erosions using a semiquantitative scoring system for effusion, synovial thickening, erosion and power Doppler signal (49). With respect to RA, identification of patients with a poor prognosis at presentation, differentiation between inactive fibrotic joint tissue from pannus and quantification of synovitis will all be important areas of investigation. PD is likely to play an important part in these respects. Additionally, contrast agents may become the equivalent of gadolinium in MRI, allowing the development of transit time curves, bolus arrival times, time to maximum intensity, area under the curve, and wash in/wash out characteristics which may further improve the characterization of inflammation. Microbubble-specific imaging modes such as harmonic imaging, extended field of view, and transmission US, as well as 3D and 4D US, offer other exciting possibilities for the future.

MAGNETIC RESONANCE IMAGING
Like US, interest in the use of MRI in rheumatology has grown dramatically over the last decade, in part due to the superior imaging of MRI but also to increased access to MRI scanners. The application of MRI in relation to early RA will be reviewed with special emphasis on its use in understanding the pathogenesis, diagnosis and monitoring response to therapy.

Definitions of MRI pathology in early RA
As a result of differences in MRI technologies, there have been differences in definitions for the common MRI RA abnormalities (e.g., bone erosions, bone oedema, synovitis and tenosynovitis). This makes comparison between studies rather difficult. In the last few years, the Outcome Measurement in Rheumatology Clinical Trials (OMERACT) international consensus group has focused on this issue and provided recommendations for standard definitions (50). These definitions were recently refined and are presented in Table I (51). It is worth considering these definitions when interpreting MRI studies and in the discussions below.

Table I. Definition of MRI pathological lesions in rheumatoid arthritis (51).

MRI pathology	Definition
Synovitis	An area in the synovial compartment with above normal post-gadolinium enhancement and thickness greater than the normal synovium
Bone erosion	A sharply marginated lesion with correct juxta-articular location and typical signal changes, with visibility in 2 planes and cortical break in at least one plane
Bone oedema	A lesion within the trabecular bone with ill-defined margins and signal characteristics of increased water content.

MRI comparisons with other imaging modalities

The earliest studies using MRI in RA examined the sensitivity of MRI in detecting the typical RA pathology. Issues of face content and construct validity have been addressed by comparison with both clinical examination and other modalities of imaging. Over the last few years, these comparison publications have included some longitudinal evaluations of MRI abnormalities.

Erosions

A key issue in the use of MRI concerns the relationship between MRI erosions and CR erosions. It is important to consider that MRI visualises protons, not calcified cortex as in CR. The particular bone abnormality seen on MRI will depend on the acquired sequences and bone oedema can complicate the reader's assessment. Wakefield *et al.* have demonstrated that T1 weighted lesions with loss of trabecular bone correlate 100% with sonographic-determined cortical breaks in the 2nd MCP joints of RA patients, where US has its best access (17). Furthermore, these lesions seem to be specific for RA: a cross-sectional comparison showed they are very infrequent in normal controls compared with RA patients (52) and, in a one-year longitudinal study of RA and early unclassified polyarthritis, MRI erosions were only found in patients with baseline RA or patients fulfilling the ACR RA criteria at one year (53). In a study of wrists from 42 early RA patients followed over 2 years, McQueen *et al.* demonstrated that MRI erosions predicted the presence of CR erosions at 1 and 2 years, but only 1 in 4 erosions became CR evident over a year (54). It is of course likely that CR will never detect all MR erosions due to its lack of tomography. In a study comparing extremity MRI (E-MRI) of the 2nd to 5th MCP joints of 25 early RA patients with CR (55), E-MRI detected 9.5 times more erosions.

Synovitis

Synovitis is probably best imaged using the paramagnetic contrast agent gadolimium (Gd-DTPA) in MRI and comparing pre- and post-gadolinium films. Gadolinium-enhanced synovial tissue has been positively correlated with macroscopic and microscopic (cellular infiltrates, fibrin deposition, vascular proliferation) changes of inflammation in the knees of RA patients (56, 57). Recently, gadolinium-enhanced synovitis has also been strongly correlated with mini-arthroscopic synovial scores in RA MCP joints (58). A preliminary report has demonstrated the advantages of gadolinium-containing over certain non-gadolinium sequences in the detection of synovitis in the wrists and MCP joints (59). However, moderate inter-reader agreement was still achieved and the use of gadolinium must be considered in the context of feasibility.

The quantification of synovitis may be semi-quantitative or quantitative. The semi-quantitative scoring methods for wrist and MCP joints are suggested in Table I (51). Conaghan *et al.* showed that semi-quantitative quantification of synovitis correlated well with more complex automated methods (60). Quantitative estimation may be:

(a) Volumetric, using manual outlining on post-gadolinium scans or semi-automatic using subtraction of pre- and post-gadolinium scans and employing thresholds (61). The manual volume methods are probably the nearest to a "gold" standard but laborious and time consuming.

(b) Acquired using Dynamic Enhanced MRI (DEMRI), which utilises post contrast analysis to determine pharmacodynamic (maximal enhancement, initial rate of enhancement) (62) and even pharmacokinetic (63) parameters.

With respect to detecting synovitis, a growing number of studies have demonstrated the improved sensitivity of MRI over clinical examination in early (64) RA. Goupille *et al.* reported MRI examination of 12 active RA patients who had wrists, MCP and PIP joints scanned (65). The clinical swollen joint count was 59 whereas MRI detected synovitis in 162 joints. This sensitivity is similar to our data on MCP joints alone in early disease (21) and more recently in patients in clinical remission (37). Goupille *et al.* also demonstrated significant associations between MRI synovitis and the swollen joint count, Ritchie Index, the disease activity score and early morning stiffness. E-MRI has also been demonstrated to be more sensitive than clinical examination in a study of over 100 MCP joints and showed synovial thickening in 51% of the clinically inactive joints (54).

Tendons

Flexor and extensor tenosynovitis is an important contributor to hand and feet problems in RA. This area of RA pathology has been less well studied than erosions and synovitis. Both clinical and MRI definitions of tenosynovitis are problematic. However, Hug *et al.* reported a study of 11 RA patients using fat-suppressed MRI images at the MCP level and defining flexor tenosynovitis as a rim of high signal intensity around the tendon (66). They demonstrated a high frequency of tenosynovitis. A recent study of wrist tendons from 43 established RA patients (with active disease and no clinical tendon tears) and 12 healthy controls focused on both the intra-tendon signal and tendon sheath thickness (67). Over one half of the wrist tendons in the RA group had evidence of increased sheath thickness (presumed tenosynovitis) and

only 46% had normal tendons. The greatest abnormalities were seen in the dorsal and ulnar tendon sheaths. Another study of MCP and PIP joints in early RA demonstrated a high frequency of MRI tenosynovitis (68).

MRI in understanding RA pathogenesis

One of the major insights derived from MRI for the pathogenesis of inflammatory arthritis has come out of studies by McGonagle *et al.* suggesting 2 subgroups of patients: a primarily intra-synovial group (RA) and an entheseal-based group (for example the spondyloarthropathies and polymyalgia rheumatica) (68-70). Importantly, further insights into RA pathogenesis have now been gained from the use of MRI.

Synovitis and bone damage

For many years, there was confusion about the relationship between synovitis and bone erosions, as CR studies had demonstrated the progression of erosion despite apparent clinical control of inflammation (71, 72) and the dampening of the erosion progression even though there was little change in clinical synovitis (73). Later studies demonstrated that effective disease suppression did reduce bony damage (74, 75) and a CR study examining tender and swollen hand joints in early RA patients demonstrated a close relationship between these clinical surrogates and bone erosion progression (76). Studies employing MRI have been able to visualise more closely this relationship. Preliminary information on the prognostic value of gadolinium-enhanced synovitis for predicting erosions in the small finger joints of established RA patients was reported by Jevtic *et al.* in 1996 (77). Huang *et al.* using DEMRI in early RA patients demonstrated that the severity of synovitis predicted MRI erosion as well (78). Using the MCP joints (where the relationship between synovitis and bone damage is easier to visualise at the individual joint level) in 40 early RA patients, Conaghan *et al.* were able to demonstrate that erosion progression was proportional to the level of synovitis in a given joint, and that no erosions occurred in joints without synovitis (79).

The MRI-visualised link between synovitis and MRI erosion appears to be bone oedema. Bone oedema is frequently present in new, untreated RA but only infrequently seen in normal controls (80). This finding has recently been confirmed with the observation that RA but not polyarthralgia patients demonstrate bone oedema (81). In a cross-sectional study of 31 early RA patients, bone oedema was almost exclusively seen in joints with synovitis (80). In a longitudinal evaluation of a different cohort of 40 patients, the synovial thickness was greater in those joints with bone oedema than those without (79). In the same study bone oedema was shown to precede subsequent MRI erosions in approximately 40% of new erosions. A relationship of bone oedema to disease duration in the hand joints of RA patients has been reported, probably reflecting the same process (i.e., persistence or severity of synovitis causing bone oedema and consequent erosion) (82). This finding was confirmed in a longitudinal study showing that bone oedema in the wrist is predictive for bone erosions at 12 months (83). It is important to note that, at the level of bone oedema, bone damage appears to be reversible (see Outcomes section below).

Joint mechanics and architecture

Study of the intra-joint site of erosions with MRI has also increased understanding of the pathogenesis of erosions. A case-control study of RA wrists demonstrated that carpal bone damage becomes asymmetric over time with more damage being evident on the radial, force-bearing side of the wrist (84). Recently a detailed study of 40 early RA patients demonstrated a predilection for radial involvement in the 2nd to 4th MCP joints, by scoring the site of erosions and using DEMRI techniques to ascertain synovitis volumes adjacent to MCP joint collateral ligaments (85). The role of biomechanical factors in relation to synovitis and erosions is thus becoming clear. MRI also opens up the possibility of a highly detailed understanding of joint architecture.

MRI and the diagnosis of RA

Early diagnosis with consequent early treatment is now the hallmark of RA management (86). With the reported sensitivity of MRI in detecting erosions and synovitis, and the apparent specificity of bone oedema changes, it follows that MRI should aid in the early diagnosis of RA. In a recent study, Boutry *et al.* showed that MRI of the feet detects as much synovitis, tenosynovitis and bony changes as MRI of the hands in early RA (87) and suggested that MRI of the feet may be useful when evaluation of hands does not help to identify early RA. However, there has still been limited work on the impact of MRI in this area, reflecting the poor access to MRI, a paucity of knowledge on the critical number or sites of joints to image, and the growing ability of ultrasonography to easily image multiple joints in real time. Using baseline bilateral total hand contrast-enhanced MRI, Sugimoto *et al* followed 50 patients with polyarthralgia for over 2 years and evaluated the ACR diagnostic criteria for RA (88). Comparing MRI-based criteria with the ACR criteria, they reported that MRI had a sensitivity of 96%, specificity of 86% and accuracy of 94%. They then suggested combining imaging criterion with the existing classification tree criteria in order to decrease the false-negative diagnosis of RA. Further evaluation of such criteria will be required.

MRI as an outcome measure in RA therapy evaluation

The sensitivity of MRI to the key elements in RA pathology suggests that the sample size of studies for new therapies and proof-of-concept could be smaller. However, as indicated in the 'Definitions' section above, there is a need to address issues of reliability and sensitivity to change before the widespread adoption of MRI in clinical trials (89). The OMERACT RA-MRI group has presented and updated definitions on lesions and has been further involved in exercises to determine inter-reader reliability using these definitions. While this work is ongoing and iterative, there has generally been excellent agreement when 1 or 2 readers

Table II. Advantages and disadvantages of ultrasonography.

Advantages of ultrasound	Disadvantages of ultrasound
1. Relatively inexpensive	Operator dependant and steep learning curve
2. Available in most radiology departments and increasingly available in many rheumatology departments	Limited transducer access, for example, for deep joints such as the hip or more superficial joints where adjacent joints are in close proximity such as carpal bones
3. Potential immediate availability in outpatient departments enabling rapid decision making	Limited data on sensitivity to change with treatment
4. Ability to scan several joints at one timepoint	Additional time required in the clinical setting
5. Well tolerated	Lack of standardized methodology
6. No ionising radiation, allowing multiple assessments in time and place	
7. Relative short scanning time (all joints < 40 mins, hands and feet 5 mins)	
8. Allows real time, dynamic joint assessments	
9. Portable	

Table III. Advantages and disadvantages of MRI.

Advantages of MRI	Disadvantages of MRI
1. Multiplanar	Expensive (equipment, running and personnel costs)
2. No ionising radiation	Time consuming (e.g. hand and wrist takes approximately 50 mins.)
3. Considered the gold standard	Limited to one anatomical site/examination
4. More sensitive than clinical examination, X-ray and US for the detection of synovitis and erosions	Not well tolerated by some patients who are anxious and claustrophobic (some may require sedation); problematic for elderly who find it difficult to lie flat or still; unsuitable for patients with ferromagnetic devices/implants such as heart valve
5. Standardised imaging protocols and sequences	High level of expertise required
6.	Motion artefacts
7.	? Too sensitive (i.e., uncertainty about the clinical significance of findings)
8.	Artefacts around non-ferromagnetic metal orthopaedic hardware

are employed, with moderate agreement in 5-reader studies (90). These reliability studies have recently evaluated longitudinal scoring and demonstrated intraclass correlation coefficients and smallest detectable difference values similar to those of standard RA outcomes (clinical and CR) (91).

With respect to drug outcome studies, the earliest studies provided proof of MRI's ability to measure change in synovial volume after a known effective therapy, generally corticosteroid injections (92). The Leeds group has reported 2 studies using DEMRI to assess response in the knee joint in evaluating anti-CD4 and in comparing methotrexate and leflunomide treatments; both of these studies were performed in patients with established RA (93). In early RA, the Leeds group used semi-quantitative scoring methods to report the efficacy over 12 months of methotrexate versus methotrexate plus intra-articular corticosteroids (40 patient randomised study (83)), high dose infliximab with methotrexate (5 patient

open study (79)) and methotrexate versus methotrexate and standard dose infliximab (20 patient randomised trial, preliminary report only (94)). These studies demonstrate that MRI can, with appropriate scientific rigour, be used effectively as an outcome measure.

Conclusion

Imaging technology continues to change and is improving rapidly. New hardware, software and falling costs will change the usefulness and availability of both US and MRI. Each modality should be considered complementary to the other as each has a number of advantages and disadvantages (Tables II and III). Automated synovitis estimations and the development of dedicated extremity scanners will improve MRI's usefulness to clinicians and researchers. Well-designed validation studies are delineating the role for US in the diagnosis and monitoring of early RA and its real-time advantages make it well suited for use in out-patient settings. The application of new

imaging techniques to the early diagnosis and evaluation of treatment response heralds an era where rheumatologists will be able to better target and reduce synovitis and consequently improve RA patient outcomes.

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